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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/685,942	10/14/2003	Hon-Wah Man	9516-205-999	7683

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EXAMINER	
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1614	

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12/28/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/685,942	MAN ET AL.	
	Examiner	Art Unit	
	Charlesworth Rae	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5,7 and 8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 5, and 7-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgement is made of applicants' filing of the instant application as a Request for Continued Examination (RCE) under 37 CFR 1.1114, received 10/31/07. By Amendment filed 10/31/07, claims 7-8 have been added.

Applicant's memoralization of the Interview of October 9, 2007, is acknowledged.

Status of the Claims

Claims 1, 5, and 7-8 are currently pending in this application and are the subject of the Office action.

Terminal Disclaimer

It is noted that the terminal disclaimer filed 10/31/07 with respect to US Patent 6,667,316 is approved.

Information Disclosure Statement

It is noted that applicant is required to file an information disclosure regarding the references referred to in the response filed 10/31/07 along with a statement pointing out the relevancy of each reference listed therein.

Response to applicant's arguments/remarks

Obviousness-Type Double Patenting (ODP) rejection (claims 1 and 5)

This rejection is withdrawn in view of the approval of applicant's terminal disclaimer with respect to US Patent 6,667,316 ('316 patent).

Enablement rejection under 112, first paragraph

Applicant contends that this rejection should be withdrawn for essentially the following reasons

1) The examiner has failed to provide any evidence or reasoning under the current legal principles to rebut the presumption of enablement with respect to the instant claimed invention.

2) The PDE IV data disclosed in the instant application supports the fact that the instant invention is enabled

3) The examiner's reliance on Bielekova as the reason to doubt the presumption of enablement amounts to a "requirement that is being made of applicant to prove the ultimate value in humans."

4) Contrary to the examiner's assertion, the facts in Brana are indistinguishable for the facts in the instant case.

5) Applicant provides the following as further evidence in support of the enablement of the instant invention:

> In addition, for further evidence, Applicants submit herewith the following references, each of which shows that PDE IV is implicated in the treatment of various autoimmune or inflammatory diseases4: 1) Burnouf *et al., Curr. Pharm. Des.,* 8(14): 1255-96 (2002), which indicates that the PDE IV activity is associated with a wide variety of diseases related to inflammatory state or autoimmune pathology *(see, e.g.,* Abstract); 2) Dastidar *et al., Curr. Opin. Investig. Drugs,* 8(5): 364-72 (2007), which indicates that PDE IV inhibitors' therapeutic potential in the treatment of various inflammatory disease such as asthma, COPD, psoriasis, rheumatoid arthritis, and inflammatory bowel diseases, e.g., Crohn's disease and ulcerative colitis *(see, e.g.,* Abstract); and 3) Sommer *et al., J. Neuroimmunol.,* 79(1): 54-61 (1997), which indicates that PDE IV inhibition is advantageous for the treatment of autoimmune diseases such as multiple sclerosis *(see, e.g.,* Abstract). Therefore, as these additional references clearly demonstrate the therapeutic potential of PDE IV inhibition in a wide variety of autoimmune or inflammatory diseases, Applicants respectfully submit that the pending claims are adequately enabled[5].

In response, the rejection is maintained for the reasons made of record in the Office action mailed 9/10/07 at pages 4-8, and 11-18, and for the additional reasons set forth below:

a) Instant claim 1 is very broad and encompass a multiplicity of compounds of formula I which exhibit different and/or varying pharmacologic and pharmaceutical activities. For example, applicant discloses that formula I encompasses compounds that possess a center of chirality, which includes chirally pure (R) and (S) isomers as well as mixtures (including but not limited to racemic mixtures). See specification at page 10, line 10 to page 21, line 7, especially, page 20, last paragraph. Also, claims 1, 5, 7, and 8 encompass a multiplicity of PDE-IV related and unrelated diseases. Besides, the PDE-IV related diseases encompassed by the instant invention represent a diverse group of clinical pathologies, which are each treated via different treatment modalities. The term *"[a] method for reducing elevated levels of PDE IV in mammal"* as recited in claims 1 and 7 is reasonably construed to read on normal physiologic functions because the step of administering an effective amount of a compound of formula I does not require the presence any pathologic condition. While the term *"[a] method of treating an inflammatory disease or an autoimmune disease in a mammal"* is reasonably interpreted to encompass any and all inflammatory and autoimmune diseases independent of any PDE-IV reducing effects of a compound of formula I. In fact, applicant asserts that the compounds of formula I are useful for treatment or prophylaxis of topical disease states mediated or exacerbated by excessive TNFα production, such

as viral infections, for example those caused by the herpes viruses or viral conjunctivitis, psoriasis, other skin disorders and diseases, etc. (page 23, line 24 to page 24, line 26).

b) Contrary to applicant's statement that the facts in *Brana* are virtually identical to those in the instant case, the facts of the instant case are considered to be clearly distinguishable from those in *Brana.* First, the issue of law raised in *Brana* was whether "asserted utility" was a proper test for determining enablement under 112, first paragraph. No issue of "asserted utility" are present in the instant case and there is no requirement that is being made of applicant to prove the ultimate value in humans. The basic inquiry in this case is whether the instant disclosure teaches those skilled in the art how to make and use the instant invention commensurate with the full scope of the claimed invention without undue experimentation.

Second, the facts at issue in Brana are also distinguishable from the facts of the instant case. In the instant case, the claims are very broad and encompass a diverse group of inflammatory and autoimmune diseases that are characterized by different immunopathologies, etiologies, and clinical manifestations as evidenced by the teaching of Harrison's textbook (Harrison's Principles of Internal Medicine (1994), pages 1543-1566; see specifically Tables 277-1 and 277-2). Unlike in *Brana*, wherein a well-recognized mouse model was used to determine the anti-cancer activity of the compounds against specific species of cancer, no *in vitro* model is well recognized in the art for reliably and predictably determining the anti-PDE IV activity of the instant claimed compounds against a specific disease species or the genus of inflammatory and autoimmune diseases. Furthermore, the art teaches that PDE IV and PDE III etc.

exert complex immunomodulatory effects and raises doubts regarding whether the concentration of PDE inhibitors necessary to inhibit PDE levels *in vitro* models can be extrapolated to *in vivo* systems i.e. humans. To reiterate (see Office action mailed 01/24/07, pages 8-10),

> In particular, Bielekova et al. disclose that hyperactive Th1-mediated immune responses are thought to be involved in the pathogenesis of many autoimmune

diseases (Bielekova et al. Therapeutic potential of phosphodiesterase-4 and 3-inhibitors in Th1-mediated autoimmune diseases. The Journal of Immunology, 2000, 164:1117-1124, see page 1117, column 1, lines 1-3). Immune cells predominantly express families PDE 4, PDE3, and, to a lesser extent, PDE7 (page 1117, column 1, lines 6-8). Inhibitors of PDE4 and PDE3 families exert complex immunomodulatory properties (page 1117, column 1, lines 8-10). In animals, these drugs inhibit Ag-mediated T cell proliferation and skew the T cell cytokine profile toward a Th2 phenotype by down-regulating the expression or production of Th1 cytokines and have no effect or even augment the production of Th2 cytokines (page 1117, column 1, lines 10-14). These properties render PDE inhibition a candidate therapy for Th1-mediated autoimmune disorders (page 1117, column 1, lines 14-16). Bielekova et al. further disclose that the **simple extrapolation of therapeutic efficacy from animal models to human disorders is not easily feasible** ... (page 1117, column 1, lines 19-23). Although there is some evidence for a preferential inhibition of proinflammatory cytokines in Th1-mediated human autoimmune conditions, data from asthmatic and atopic individuals reached almost opposite conclusion (page 1117, column 2, lines 2-7). Bielekova et al. disclose that the question remains of whether the immunomodulatory effect of PDE IV inhibitors is expressed within a concentration range that is achievable in humans in vivo (page 1123, column 1, last paragraph, lines 1-5). Well designed therapeutic trials supported by immunological studies should not only provide more definite information about the therapeutic potential of PDE inhibitors in autoimmune disorders, but also broaden our understanding of the immunopathogenesis and the

potentail differences among individual human TH1-mediated autoimmune diseases (page 1123, column 2, last paragraph).

Rejections

Claim Rejections – 35 USC 112 – First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 5, and 7-8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate with the full scope of the claims. This is a scope of enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fd. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if its is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the

determination of how to practice a desired embodiment of the claimed invention. PPG v Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth in *In re Wands,* 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman* 230 USPQ 546 (BdApls 1986) at 547 the court cited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence or absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art,

7) the predictability of the art, and

8) the breadth of the claims

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

1. <u>The nature of the invention, state and predictability of the art, and relative skill of those in the art</u>.

The invention in general is directed towards a method of reducing elevated levels of PDE IV (claim 1), and a method of treating an inflammatory or an autoimmune disease (claim 5), in a mammal, comprising administering an effective amount of a compound of formula I or an acid addition salt or a substantially chirally pure isomer thereof. The relative skill of those in the art is high, generally that of an M.D. or Ph.D. It is noted that the pharmaceutical art is generally unpredictable, requiring each embodiment to be individually assessed for therapeutic activity. The more unpredictable an area, the more specific enablement is necessary in order to satisfy the statue. (see *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970)). For example, the mode of action of immunomodulatory agents is often unknown or very unpredictable and administration of such agents is often accompanied by undersirable effects. The immunopathogenesis of inflammatory and autoimmune diseases is considered to be very complex and varies widely, depending on the particular inflammatory or autoimmune disease. The therapeutic modalities also vary widely depending on the particular inflammatory or autoimmune disease. Besides, there is a disproportionately sparse number of discovery of new and predictable treatments for inflammatory and autoimmune diseases compared with the vast number of new drugs discovered.

The above discussion of the enablement rejection in connection with the Response to applicant's arguments is incorporated by reference.

The specification of the instant application discloses that it is recognized that the inhibition of PDE type IV is particularly effective in both the inhibition of inflammatory mediator release and the relaxation of airway smooth muscle and that compounds that

inhibit PDE IV specifically, would exhibit the desirable inhibition of inflammation and relaxation of airway smooth muscle with a minimum of unwanted side effects, such as cardiovascular or anti-platelet effects (page 9, lines 15-22). Applicant further discloses that currently used PDE IV inhibitors lack the selective action at acceptable therapeutic doses. Applicant asserts that compounds of the instant invention are useful in the inhibition of phosphodiesterase, particularly PDE II and PDE IV, and in the treatment of disease states mediated thereby, including inflammatory, infectious, immunological and malignant diseases (page 9, line 22 to page 10, line 9).

Also, applicant discloses a number of methods for preparing the instant compounds of formula I (page 13, line 15 to page 20, line 16). Applicant discloses that the compounds possess a center of chirality and thus can exist as optical isomers (page 20, lines 17-18). Applicant also discloses that inhibition of PDE III, PDE IV, TNFα and NFκB by the instant compounds of general formula I can be conveniently assayed by using methods known in the art (page 21, lines 4-7). Applicant discloses various methods of treatment by administering to a mammal an effective amount of a substantially chirally pure ®- or (S)-isomer of a compound of instant formula I or a mixture of those isomers (page 24, 10-23). Applicant further discloses that while these treatment methods may overlap, they also may differ in terms of method of administration, dose level, dosage regimen (such as single or multiple doses), and concurrently administered therapeutic agents (page 24, lines 23-26).

As applicant states in the response filed June 28, 2006, that "a specification disclosure ... must be taken as being in compliance with the enablement requirement ...

unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." In the instant case, there is reason to doubt the objective truth of the statements contained in the specification.

In particular, Bielekova et al. disclose that hyperactive Th1-mediated immune responses are thought to be involved in the pathogenesis of many autoimmune diseases (Bielekova et al. Therapeutic potential of phosphodiesterase-4 and 3-inhibitors in Th1-mediated autoimmune diseases. The Journal of Immunology, 2000, 164:1117-1124, see page 1117, column 1, lines 1-3). Immune cells predominantly express families PDE 4, PDE3, and, to a lesser extent, PDE7 (page 1117, column 1, lines 6-8). Inhibitors of PDE4 and PDE3 families exert complex immunomodulatory properties (page 1117, column 1, lines 8-10). In animals, these drugs inhibit Ag-mediated T cell proliferation and skew the T cell cytokine profile toward a Th2 phenotype by down-regulating the expression or production of Th1 cytokines and have no effect or even augment the production of Th2 cytokines (page 1117, column 1, lines 10-14). These properties render PDE inhibition a candidate therapy for Th1-mediated autoimmune disorders (page 1117, column 1, lines 14-16). Bielekova et al. further disclose that the **simple extrapolation of therapeutic efficacy from animal models to human disorders is not easily feasible** ... (page 1117, column 1, lines 19-23). Although there is some evidence for a preferential inhibition of proinflammatory cytokines in Th1-mediated human autoimmune conditions, data from asthmatic and atopic individuals reached almost opposite conclusion (page 1117, column 2, lines 2-7). Bielekova et al. disclose that the question remains of whether the immunomodulatory

effect of PDE IV inhibitors is expressed within a concentration range that is achievable in humans in vivo (page 1123, column 1, last paragraph, lines 1-5). Well designed therapeutic trials supported by immunological studies should not only provide more definite information about the therapeutic potential of PDE inhibitors in autoimmune disorders, but also broaden our understanding of the immunopathogenesis and the potentail differences among individual human TH1-mediated autoimmune diseases (page 1123, column 2, last paragraph).

The unpredictability or uncertainty in the art is illustrated by the fact that there is some evidence to show a preferential inhibition of proinflammatory cytokines in Th1-mediated human autoimmune conditions, data from asthmatic and atopic individuals reached almost opposite conclusion (Buelekova et al., page 1117, column 2, lines 2-7). Thus, one skilled in the art would not be able to predictably extrapolate the disclosed teachings of the claimed invention to inflammatory and autoimmune diseases with any reasonable degree of certainty.

The breadth of the claims

The claims are very broad. For example, claims 1 encompasses all mammalian species, multiple variants of the elected compound, cyclopropyl-N-{2-[1(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-3-oxoisindolin-4-yl}carboxamide, various diverse conditions involving unregulated angiogenesis, including a heterogenous group of inflammatory and autoimmune diseases that are characterized by different immunopathologies and etiologies. Although new claims 7 and 8 are directed to a single chemical compound, how the chemical feature of said compound

relates to the multiplicity of immunopathologies encompassed by these claims are unclear. Because the therapeutic response to be achieved would necessarily vary depending upon the specific inflammatory or autoimmune disease that is intended to be treated, the level of predictably in practicing the claimed invention would be greatly diminished.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides limited direction or guidance for determining the particular administration regimens (dosages, timing, administration routes etc.) necessary to treat all inflammatory and autoimmune diseases associated with unregulated angiogenesis. The 'working examples" are limited to in vitro experiments. Thus, the applicant at best has provided specific direction or guidance only for an in vitro methodology for evaluating PDE IV inhibitory effects of the elected compound of instant general formula I. No reasonably specific guidance is provided concerning useful therapeutic protocols for treating inflammatory and autoimmune diseases.

4. The quantity of experimentation necessary

In view of applicant's disclosure that the treatment methods while they may overlap, they also may differ in terms of method of administration, dose level, dosage regimen (such as single or multiple doses), coupled with the complex and different immunopathologies associated with inflammatory and autoimmune diseases (page 24, lines 23-26), it is reasonable to surmise that this level of uncertainty and

unpredictability in the art would require one skilled in the art to conduct more than routine experimentation in order to practice the claimed invention as claimed.

For the reasons stated above, claims 1, 5, and 7-8 are rejected under 35 USC 112, first paragraph, for lack of enablement because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention as claimed.

Newly applied Obviousness-Type Double Patenting (ODP) rejection

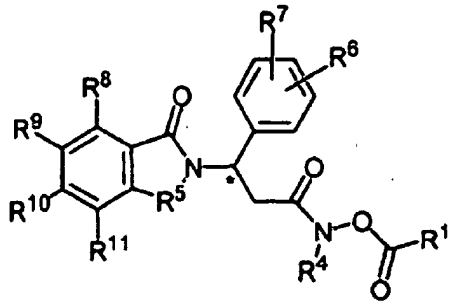
The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 5, and 7-8 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 47-70 of copending U.S. Patent Application No. 10/786,822 (appl. '822). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are either anticipated by, or would have been obvious in view of the referenced claims.

In particular, claim 47 of appl. '822 14 recites a method inhibiting PDE-4, TNF-α, MMP, or undesired angiogenesis in a mammal comprising administering an effective amount of a compound of below formula I or II:



I

wherein:

the carbon atom designated * constitutes a center of chirality;

R^4 is hydrogen or -(C=O)-R^{12};

each of R^1 and R^{12}, independently of each other, is alkyl of 1 to 6 carbon atoms, phenyl, benzyl, pyridyl methyl, pyridyl, imidazoyl, imidazolylmethyl, or $CHR^{\bullet}(CH_2)_nNR^{\bullet}R^0$, wherein $R^{\bullet}$ and R^0, independently of the other, are hydrogen, alkyl of 1 to 6 carbon atoms, phenyl, benzyl, pyridylmethyl, pyridyl, imidazoyl or imidazolylmethyl, and n = 0, 1, 2;

R^5 is C=O, CH_2, -CH_2-CO-, or SO_2;

each of R^6 and R^7, independently of the other, is nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, cycloalkoxy of 3 to 8 carbon atoms, halo, bicycloalkyl of up to 18 carbon atoms, tricycloalkoxy of up to 18 carbon atoms, 1-indanyloxy, 2-indanyloxy, C_4-C_8-cycloalkylidenemethyl, or C_3-C_{10}-alkylidenemethyl; and

each of R^8, R^9, R^{10}, and R^{11} independently of the others, is

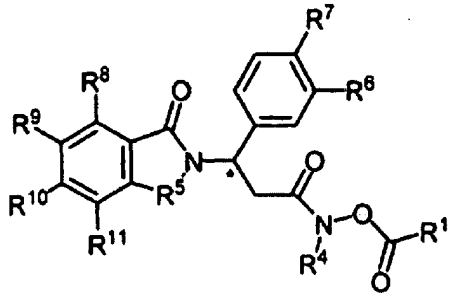
(i) hydrogen, nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkylamino, dialkylamino, acylamino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, halo,

(ii) one of R^8, R^9, R^{10}, and R^{11} is acylamino comprising a lower alkyl, and the remaining of R^8, R^9, R^{10}, and R^{11} are hydrogen,

(iii) hydrogen if R^8 and R^9 taken together are benzo, quinoline, quinoxaline, benzimidazole, benzodioxole, 2-hydroxybenzimidazole, methylenedioxy, dialkoxy, or dialkyl,

(iv) hydrogen if R^{10} and R^{11}, taken together are benzo, quinoline, quinoxaline, benzimidazole, benzodioxole, 2-hydroxybenzimidazole, methylenedioxy, dialkoxy, or dialkyl, or

(v) hydrogen if R^9 and R^{10} taken together are benzo; or



II

wherein:

the carbon atom designated * constitutes a center of chirality;

R^4 is hydrogen or -(C=O)-R^{12},

where each of R^1 and R^{12}, independently of each other, is alkyl of 1 to 6 carbon atoms, phenyl, benzyl, pyridyl, pyridyl methyl, imidazolyl, imidazoylmethyl, or $CHR^*(CH_2)_nNR^*R^0$

wherein R^* and R^0, independently of the other, are hydrogen, alkyl of 1 to 6 carbon atoms, phenyl, benzyl, pyridylmethyl, pyridyl, imidazoyl or imidazolylmethyl, and n = 0, 1, 2;

R^5 is C=O or CH_2;

each of R^6 and R^7, independently of the other is alkoxy of 1 to 8 carbon atoms, cycloalkoxy of 3 to 6 carbon atoms; C_4-C_6-cycloalkylidenemethyl, C_2-C_{10}-alkylidenemethyl, C_6-C_{18}-bicycloalkoxy, C_6-C_{18}-tricycloalkoxy, 1-indanyloxy, or 2-indanyloxy;

each of R^8, R^9, R^{10}, and R^{11}, independently of the others, is hydrogen, nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, halo, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkylamino, dialkylamino, acylamino, alkyl of 1 to 10 carbon atoms, and alkoxy of 1 to 10 carbon atoms.

Thus, the instant claims 1, 5, and 7-8 are deemed to be obvious variants of the the referenced claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Charlesworth Rae whose telephone number is 571-272-6029. The examiner can normally be reached between 9 a.m. to 5:30 p.m. Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached at 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http:pair-direct.uspto.gov. Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 800-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

20 December 2007
CER

BRIAN-YONG S. KWON
PRIMARY EXAMINER